USAID

INFECTIOUS DISEASE INITIATIVE

STRATEGIES AND INTERVENTIONS TO UNDERSTAND, CONTAIN, AND RESPOND TO THE DEVELOPMENT AND SPREAD OF

ANTIMICROBIAL RESISTANCE

Activities initiated in FY99[1]

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[1] This document contains only those activities that were initiated with FY99 funding from USAID. Activities started in FY98 (and receiving additional funding in FY99) are listed in a separate document.

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LIST OF ABBREVIATIONS

AIHA	American International Health Alliance
APUA	Alliance for the Prudent Use of Antibiotics
CDC/NCID	Centers for Disease Control and Prevention/National Center for Infectious Diseases
HIID/ARCH	Harvard Institute for International Development/Applied Research on Child Health
ICDDR/B	International Centre for Diarrheal Disease Research, Bangladesh: Centre for Health and Population Research
INCLEN	International Clinical Epidemiology Network
INRUD	International Network for the Rational Use of Drugs
JHU/FHACS	Johns Hopkins University/Family Health and Child Survival
MSH	Management Sciences for Health
PAHO	The Pan American Health Organization
QAP II	Quality Assurance Project II (USAID)
RPM	The Rational Pharmaceutical Management Project (USAID)
USP	The United States Pharmacoepial Convention
WHO/CAH	World Health Organization/Child and Adolescent Health (includes the division previously named Child Health and Development [CHD])
WHO/CDS	World Health Organization/Communicable Diseases (includes the division previously named Emerging and other Communicable Diseases Surveillance and Control [EMC])
WHO/HTP/EDM	World Health Organization/Health Technology and Pharmaceuticals/Essential Drugs and Medicines (includes the divisions previously named Action Programme on Essential Drugs [DAP] and Drug Management and Policies [DMP])

AMR Component #1: Establishing a Global Strategy and Implementation Plan

1.6 Title: Synthesis of Sentinel Policy Documents Concerning Strategies for Curbing AMR

Implementing Organization: Alliance for the Prudent Use of Antibiotics

Rationale: Expert study groups such as the American Society for Microbiology, Infectious Diseases Society of America, Centers for Disease Control and Prevention, and Institute of Medicine have reported on the problem of antimicrobial resistance (AMR). Their sentinel reports identify factors that impact resistance and strategies to control its emergence and spread (see Appendix A). Viewed together, these documents represent a consensus of opinion from a variety of relevant disciplines, suggesting actions needed to curb AMR. Documentation of this consensus, as well as variance of opinions on alternate strategies, would provide a useful framework for a global strategy to combat AMR. To capitalize on the expert opinion represented, these documents should be reviewed to identify points of agreement and dissent on research needs and prevention and control strategies. By creating a single review document, APUA will provide USAID and WHO with a framework for developing a global strategy to improve the use of antibiotics and contain AMR.

Objective: Review the expert policy documents concerning strategies for curbing antimicrobial resistance*;* synthesize their conclusions and recommendations; and in conjunction with members of APUA's Scientific Advisory Board, develop a single review document, which would assist WHO and partners in the development of the global strategy.

Description: APUA staff will: (1) compile the major expert policy documents produced in both industrialized and developing countries, including selected countries from the APUA Chapter Network; (2) review and develop a brief summary of individual documents; (3) create an outline of major issues and strategies to be addressed:

- Background on AMR--issues and needs
- Prevention and control of AMR: research, prevention practices, surveillance
- Strategies and resources to control AMR: public health strategies, resources for research and data-collection
- Legal, ethical, and regulatory issues related to controlling AMR
- Conclusions and recommendations;

(4) develop a single review document identifying areas of agreement and disagreement; (5) create tables that systematically summarize the information from the major reports on AMR; (6) develop draft document that suggests priorities based on compilation of recommendations; (7) coordinate draft review by selected members of the APUA Scientific Advisory Board; (8) refine document based on committee's recommendations; (9) submit draft document to USAID and WHO for comments; (10); revise document; and (11) submit the final document to USAID and WHO for input into the process of global strategy formulation.

Expected Outputs, Results and Progress Indicators: Output: a review paper that synthesizes the conclusions and recommendations of the existing policy documents on AMR, reflects the insight of APUA's Scientific Advisory Board as to the global implications and strategy and suggests priority actions. Results: the report will provide an up-to-date overview of findings and recommendations

from sentinel documents produced by multidisciplinary expert groups. The document will be of use to the USAID global bureau working group, USAID missions, WHO global strategy partners and policy makers who fund the ID/AMR project. This document will contribute to the development of a framework for the global AMR strategy, and enable decision-makers at all levels to better determine future research and policy directions, and develop an action plan for controlling AMR. Progress indicators: individual reviews completed, outline of paper completed, draft paper and tables completed, meeting of scientific reviewers completed, final paper published and disseminated.

Countries/Regions: Not applicable.

Partners: None.

1.7 *Title: Reviews of Antecedents of and Interventions to Decrease Inappropriate Antimicrobial Use by Health Providers and Community Members*

Implementing Organizations: HIID/ARCH and MSH/RPM

Rationale: The 1997 International Conference on Improving Use of Medicines (ICIUM) marked a major milestone in international efforts to promote quality use of medicines by health providers and consumers, and to develop rational pharmaceutical policies. For the first time, there exists a consensus about appropriate methodologies for implementing and assessing interventions in these areas, coherent summaries of previous experience, as well as an agreed agenda of priority policy implementation and intervention research topics.

Research focused on interventions targeting the practices of physicians, paramedics, and other health providers working in primary care, hospital, or retail pharmacy setting are an important contribution, especially if it could be achieved and maintained on a widespread level in the community. However, there are two important issues which make this, on its own, unlikely to succeed. Firstly, self medication is popular in all countries. In many developing countries over 80% of all drugs are purchased by people for themselves or for a family member without prescription (Malek, A, unpublished). Secondly, whether or not consumers consult health workers in formal health care channels, it is ultimately people's own decision-making and understanding which determines whether a drug will be used or not and whether it will properly used. These decision are in turn shaped by many factors including the social, cultural and economic context in which they live and the commercial pressures to which they are exposed by marketing. When people take medicines, they do so on the basis of rational decisions which at times may contradict what ought to be done from a biomedical perspective. For example the very poor may take medicine because they have come to believe that this offers a way out of misery, hunger and pain. The contradiction between different rationalities and how to bridge them is the challenge for improving drug use in the community (Hardon, A, 1997).

This proposal calls for a comprehensive review on antecedents of and interventions to improve inappropriate antimicrobial use by health providers and community members. It is expected that this review will attempt to answer these questions: *what do we know about the factors that underlie*

inappropriate use of antimicrobials? what do we know about the structure of interventions that have attempted to improve inappropriate use? have the interventions been well-designed given the causative factors?

Objectives:

1. To identify factors that underlie inappropriate use of antimicrobials amongst health providers and community members.
2. To investigate and document the structure of interventions that have been attempted to improve inappropriate use of antimicrobials by health providers and community members.
3. To investigate whether the interventions have been designed in consideration of causative factors.
4. To recommend strategies to address key priorities in improving the inappropriate use of antimicrobials by health providers and community members.

Description: *Source of Materials:* These reviews would access all the material on both health provider and community-oriented interventions collected for the ICIUM conference. The INRUD bibliography would be a primary source for identifying supplementary materials, although the extensive collection on community use of antimicrobials at WHO/EDM and the University of Amsterdam would also be included. Additional search will also be performed within the Med-line, Pop-line database and also other related centers such as the one at the University of Groningen. For these reviews to be reasonably complete, a more active process of information gathering would be needed, since a large amount of useful material of determinants of use has never been published. For example, there is a substantial amount of unpublished materials on community use of antimalarials. This material gathering could be carried out through existing research networks as was done in collecting the ICIUM review materials.

Personnel: The review would be prepared by Dr. Aryanti Radyowijati and Dr. Hilbrand Haak, supervised by the staff from the ARCH project and RPM staff. The supervision covers comments on versions of the manuscript as it develops, and participation in the revision of the draft documents. A meeting will be held at the beginning of the review process to develop a detailed plan for the reviews, and during the revision process.

Timing: This review will require six months periods of person-works, divided into two steps. The first step is to gather the existing materials for the review, which is 2 person-months of work. And the second step for reading and writing the review, which is 4 person-months of work.

Expected Outputs, Results and Progress Indicators: Output, a review of Antecedents of and Interventions to Improve Antimicrobial Use by Health Providers and Community Members. Results: policy makers in developing countries will have access to a framework and results that will help guide policy decisions in designing strategies to encourage appropriate use of antimicrobial drugs. Progress Indicators: relevant studies identified; relevant studies reviewed; and report drafted.

Countries/Regions: The review will cover studies in Africa, Asia, Latin America and the NIS

Partners: WHO/EDM.

1.8 Title: Review of Nosocomial Infections

Implementing Organization: JHU/FHACS

(Description of activity not yet available.)

AMR Component #2: Improving the Understanding of Antimicrobial Resistance

2.12 Title: *Evaluation of the Impact of Repeated Mass Azithromycin Prophylaxis on Antimicrobial Resistance in Countries Initiating Trachoma Control*

Implementing Organization: CDC/NCID

Rationale: Mass chemoprophylaxis with azithromycin is the cornerstone of a new initiative to eliminate trachoma, a leading form of preventable blindness. Recent evidence suggests that blindness caused by the bacteria *Chlamydia trachomatis* can be prevented by a simple regimen of azithromycin along with improved hygiene. A number of African countries with high trachoma burdens are planning to implement trachoma control programs in collaboration with donor agencies (e.g. International Trachoma Initiative, Carter Center) and industry partners (Pfizer, Inc.). Control programs consist of repeated mass chemoprophylaxis of entire villages, along with educational campaigns.

In communities with limited health care access, repeated mass exposure to macrolide antibiotics may reduce the incidence of bacterial diseases in addition to trachoma, such as group A streptococcal pharyngitis, skin infections and acute rheumatic fever. However, antibiotic prophylaxis may also have the adverse effect of increasing antimicrobial resistance in both *C. trachomatis* and other bacterial pathogens. Measuring antibiotic resistance in *C. trachomatis* remains technically challenging, although there is suggestive evidence that some strains have reduced sensitivity to macrolide antibiotics. For the case of other bacterial pathogens, a study of an aboriginal population in Australia found that azithromycin treatment to control trachoma resulted in an increased prevalence of macrolide-resistant *Streptococcus pneumoniae* that persisted for months following treatment. *S. pneumoniae* is one of the leading bacterial causes of acute respiratory infections in children in the developing world. Although macrolide antibiotics are not a standard treatment for respiratory illness in developing countries, resistance to macrolide antibiotics in *S. pneumoniae* is often associated with resistance to other antimicrobial classes. This raises the concern that mass treatment programs may reduce the burden of trachoma but increase the burden of antimicrobial resistance in common respiratory tract pathogens.

Objective(s):
1. To determine the impact of mass azithromycin prophylaxis on the prevalence of antimicrobial resistant pneumococcal carriage and invasive disease
2. To institute surveillance for potential beneficial effects of community chemoprophylaxis by monitoring the incidence of: pharyngitis, skin infections, sexually-transmitted diseases, and if possible, rheumatic fever and low birth-weight infants.

3. To increase local laboratory capacity to isolate bacterial pathogens and conduct susceptibility screening.
4. If techniques are available, to determine the impact of mass azithromycin prophylaxis on the prevalence of macrolide-resistant *C. trachomatis*

Description: A single, well-defined village or region will be used as a case study for the impact of mass azithromycin prophylaxis. An appropriate village/region that is not undergoing mass chemoprophylaxis will be selected to serve as a control population. In the village undergoing chemoprophylaxis, we will swab the nasopharynx of each child <6 years of age before they receive azithromycin to determine the baseline carriage rate of antimicrobial resistant *S. pneumoniae* and *Haemophilus influenzae*. Depending on the size of the village, a follow up swab survey on all children or a subset of children will be conducted one month later and then at six month periods. Additionally, before the first mass chemoprophylaxis treatment, we will establish surveillance at the central hospital and outpatient clinic in the village for invasive pneumococcal disease, pharyngitis, skin infections, *Chlamydia trachomatis* infections (STD and trachoma), and if possible, acute rheumatic fever and low-birth weight infants. Similar surveillance will be established in the control village, and swab surveys will be conducted at the same time points as in the village receiving chemoprophylaxis.

Expected Outputs, Results and Progress Indicators: Results of this study will help clarify whether mass antibiotic treatment leads to increased antibiotic resistance among common bacterial respiratory pathogens such as *S. pneumoniae* and *H. influenzae*. If laboratory techniques are available, it will also assess whether macrolide resistance develops in *C. trachomatis*. In addition to this central question, the study will also determine whether mass antibiotic therapy reduces the incidence of health problems unrelated to trachoma, such as group A streptococcal disease. This will help countries with endemic trachoma assess the costs and benefits of initiating trachoma control programs, and will provide a general framework for evaluating the impact of mass treatment programs that can be used when future antibiotic prophylaxis interventions are proposed. Finally, because macrolide antibiotics are not commonly used in most African countries, this study will provide a foundation for understanding the spread of antimicrobial resistance in respiratory pathogens following the introduction of a new antibiotic agent. Progress indicators include the following:

- Contact with trachoma foundation initiated and timeline for introduction of mass chemoprophylaxis identified;
- Ministry of Health in appropriate country contacted, and study villages identified;
- Laboratory facilities identified, and laboratory training conducted;
- Laboratory results obtained by local personnel confirmed at reference laboratory;
- Protocol to evaluate mass chemoprophylaxis drafted and finalized;
- Baseline surveillance and nasopharyngeal carriage study initiated;
- Follow up surveillance and carriage studies at 6 month periods during 2 years of mass chemoprophylaxis campaigns;
- Study results analyzed and presented.

Countries/Regions: Countries currently implementing trachoma control programs include: Tanzania, Mali, Ghana, Niger, Yemen, Nigeria and Sudan. Implementation in Tanzania and Mali is

scheduled for 1999; in Tanzania mass chemoprophylaxis may begin as soon as late summer, 1999. Countries, such as Tanzania and Mali, that are about to initiate mass chemoprophylaxis are the most appropriate for this study.

Partners: Joe Cook Trachoma Foundation; The Carter Center; International Trachoma Initiative (ITI).

2.13 Title: Training on the Rational Use of Drugs for Pharmacy Undergraduates

Implementing Organization: WHO/HTP

Rationale: Much work has been done to improve undergraduate medical curricula. There is a great need to do the same for pharmacy undergraduate curricula in developing countries. A core curriculum for pharmacy in developing countries is needed, which includes drug management issues and the role of the pharmacist to prevent antimicrobial resistance, including promoting rational use of antimicrobials, and infection control.

Objective(s): To prepare training materials for undergraduate pharmacy students, with the intention to transfer to them the knowledge, skills and attitudes necessary to prevent antimicrobial resistance.

Description: Regional workshops with heads of pharmacy schools in Asia, Latin America and Francophone Africa; development of a document with core curriculum and practical recommendations how to review/adapt any existing curriculum; field testing of the document; production of a WHO core curriculum with relevant training materials. This is a project which will require 2-3 years to complete.

Expected Output, Results and Progress Indicators: Outputs include a WHO document with a core pharmacy curriculum, and key training materials for undergraduate pharmacy training for developing countries in English, French, Spanish and Russian. Indicators: 1999, collecting existing training materials; developing core curriculum and training materials; 2000, field testing of materials in at least three pharmacy schools in developing countries; 2001, finalizing, editing and printing of materials in English, French, Spanish and Russian.

Countries/Regions: Not applicable.

Partners: WHO Collaborating Centre on Research and Training in Pharmacy Practice, Aberdeen, Scotland; International Pharmacy Federation (FIP); pharmaceutical professional associations in developed and developing countries.

2.14 Title: AMR 'Toolkit' for Information and Education

Implementing Organization: WHO/CDS

Rationale: Effective containment of antimicrobial resistance will require the coordination and collaboration of many different stakeholders who have different levels of knowledge and understanding of antimicrobial resistance. Simple and more in-depth information, making reference to different stakeholder groups and packaged in a visually-attractive, user-friendly format can be a valuable tool for individual and group learning about resistance and ways in which it can be contained. Such a tool can also be used as a basis for advocacy.

Objective(s): To develop a multi-media tool to provide a basis for dissemination of information and advocacy about antimicrobial resistance.

Description: Communication with international partners to identify existing materials; preparation of appropriate new materials; collaboration with external technical expert to develop video and CD-ROM and to package toolkit.

Expected Output, Results and Progress Indicators: Outcomes include a tool for information, education and advocacy to: (a) rapidly inform non-specialists of key information; and (b) cover each topic more comprehensively for more specialist educational uses. Indicators include: (1) feedback from interested parties; (2) new needs identified and materials prepared; and (3) toolkit prepared and assembled.

Countries/Regions: Not applicable.

Partners: None.

AMR Component #3: Developing Methods to Detect Resistance

3.6 Title: Magnitude and Trends of Resistance in Priority Infectious Diseases

Implementing Organization: WHO/CDS

Rationale: The data that exist on the magnitude and trends of AMR are seriously lacking in quantity, quality and comparability. Furthermore there are very few studies showing trends in resistance over time, or linking in-vitro resistance to antimicrobial use or clinical outcome. For some infectious diseases (such as tuberculosis) progress has been made in establishing internationally-accepted methods for data gathering. For other diseases there is still much to do in the area of standardisation of methods. Furthermore external quality assurance is essential to the collection of valid data.
The combination of these activities for several different diseases under one project will facilitate the synergy between projects and the sharing of learning about different resistance challenges.

Objective(s):

1. To measure the magnitude and monitor trends in resistance in tuberculosis (including MDR-TB), malaria, and other priority bacterial infections;
2. To develop national capacities, provide technical assistance for resistance monitoring, and maintain international networks of reference laboratories for external quality control;
3. To disseminate information on magnitude and trends of AMR (linked to project 3.9).

Description:

1. Expand and continue to implement projects for monitoring MDR-TB in high priority countries;
2. Prepare and evaluate DRS protocols following standardised methodological guidelines. This will include technical advice, site visits and quality assessment;
3. Organise a meeting to review the data collected through monitoring of drug-resistant malaria by determining therapeutic efficacy of anti-malarial drugs;
4. Strengthen monitoring of gonococcal resistance and improve the epidemiological basis of the data collection;
5. Provide guidelines and training to enable the building/strengthening of networks to monitor other priority bacterial infections;
6. Maintain and expand as required networks of reference laboratories for quality assurance of antimicrobial susceptibility testing (incl. MDR-TB and DR-malaria)

Expected Output, Results and Progress Indicators:

1. Accurate and representative resistance data and trends in MDR-TB from 15-20 new projects validated by reference laboratories and sound epidemiological methods;
2. Report of meeting and recommendations to countries for monitoring drug resistant malaria (pending outcome of clinical trials of combination therapy);
3. Gathering of accurate and representative resistance data on drug resistance in malaria initiated and first report complete;
4. Networks for AMR monitoring in other bacterial infections strengthened in 10 countries;
5. Data sharing on AMR optimised (see project 3.9)
6. Reports from external quality assurance schemes.

Countries/Regions: To be determined.

Partners: These activities will be carried out in close collaboration with all other relevant groups in WHO/CDS cluster, especially Dept of Control and Prevention, Dept of Research and Development (TDR) and Roll Back Malaria, and with the STI/UNAIDS Working Group, with WHO Regional Offices and with the IUATLD and other external partners in public health and academic institutions around the world.

AMR Component #5: Preventing and Slowing the Spread of Antimicrobial Resistance

5.18 Title: *Evaluation of the Impact of Pneumococcal Conjugate Vaccine on Antimicrobial Resistant Streptococcus pneumoniae*

Implementing Organization: CDC/NCID

Rationale: *Streptococcus pneumoniae* is the predominant cause of bacterial pneumonia and a major cause of meningitis, sepsis, and ear infections. This organism has become increasingly resistant to multiple classes of oral and parenteral antibiotics, complicating clinical management decisions and increasing the cost of caring for children in both resource poor and developed countries. Protein-polysaccharide conjugate vaccines directed against 7, 9, or 11 pneumococcal serotypes are under investigation in several countries. A 7-valent formulation was shown to be efficacious against bacteremic disease, otitis media, and radiographically confirmed pneumonia with consolidation among infants studied in a Northern California managed care population. Preliminary studies suggest that pneumococcal conjugate vaccines reduce nasopharyngeal carriage of pneumococci due to serotypes included in the vaccine, but may increase carriage of other serotypes (nonvaccine-types). To date, the majority of pneumococci associated with penicillin resistance are caused by serotypes contained in the 7-valent formulation. In the United States, 77% of all invasive pneumococcal disease caused by penicillin nonsusceptible organisms is due to serotypes contained in the 7-valent formulation. The potential for pneumococcal conjugate vaccines to reduce nasopharyngeal colonization and therefore transmission of drug resistant pneumococci is great. While large and small-scale studies of immunogenicity and effectiveness of pneumococcal conjugate vaccine are in progress, the focus of most of these is impact of vaccine on clinical endpoints (bacteremia, otitis media, pneumonia) rather than antimicrobial resistance. Quantifying the impact of conjugate vaccine on resistant carriage will provide important data for decision-makers trying to determine potential benefits of these new prevention tools. We propose a study to be located in a community with high-prevalence of drug-resistant pneumococci designed to assess the impact of widespread introduction of pneumococcal conjugate vaccine on carriage of drug resistant pneumococci. We will focus susceptibility testing on both beta-lactam agents (e.g., penicillin, amoxicillin, or cephalosporin) and trimethoprim-sulfamethoxazole, the first line therapeutic agents for respiratory infections in most developing countries.

Objective(s):
1. To determine the impact of widespread introduction of pneumococcal conjugate vaccine on carriage of penicillin and trimethoprim-sulfamethoxazole nonsusceptible pneumococci in vaccinated infants and unvaccinated older children and adults
2. To determine the impact of widespread introduction of pneumococcal conjugate vaccine on carriage of susceptible pneumococci in vaccinated infants and unvaccinated older children and adults

Description: This project will involve carriage studies in children before and after the widespread introduction of pneumococcal conjugate vaccine. Such widespread introduction is anticipated to occur in the United States possibly as soon as early in 2000. Baseline carriage studies are available

in Alaskan native populations. This proposal is to conduct pre- and post-marketing carriage studies in areas with high levels of drug resistance (e.g., Alaskan villages) or conduct carriage studies pre- and post-vaccination in a developing country setting where vaccine is not currently being studied but where high levels of resistance make such study compelling (e.g., various Asian countries). Field studies of carriage used in this project will pilot test the consensus methods for nasopharyngeal colonization detection of drug-resistant *S. pneumoniae* as well as conform to the standards proposed by the World Health Organization committee on carriage studies used in connection with vaccine trials. The project may also offer an opportunity for field testing of components of the USAID supported laboratory manual for resistance testing.

Collaborators will consider use of cluster-design for sequential assessments of pneumococcal carriage and will include collection of simple data elements regarding relevant confounders and/or risk factors for carriage of resistant pneumococci. Young children in the community will be followed up repeatedly to assess short and longer-term impact of pneumococcal vaccination on acquisition of resistant organisms. Characterization of the serotype, and on a subset, genotyping, of pneumococcal resistant isolates will also be performed, to determine replacement carriage by nonvaccine types, and possible capsular switching between serotypes among the resistant clones.

Expected Outputs, Results, and Progress Indicators: The output of the study will be a report comparing the proportion of children before and after the introduction of conjugate vaccine to the population who are colonized with a) beta-lactam nonsusceptible pneumococci (penicillin MIC $\geq$0.12); b) beta-lactam resistant pneumococci (penicillin MIC $\geq$2); c) high level resistant organisms (MIC $\geq$4) which are considered more relevant for pneumonia treatment failures and d) cotrimoxazole nonsusceptible and resistant pneumococci. These data will fill a gap in understanding of the full impact of pneumococcal conjugate vaccines which in some areas will help overcome barriers to vaccine use. Progress indicators will include: (1) identification of partner organizations, research collaborators, and potential field setting for study; (2) development of protocol in concert with local investigators; (3) obtaining appropriate OPRR approved project assurance and IRB approvals (by local ethics committee, CDC IRB, and other partners as appropriate); (4) training of laboratory and field staff in study methods; (5) conduct vaccination and initial carriage study; (6) completion of laboratory studies on baseline carriage study; (7) analyze risk factors for resistant carriage at baseline; (8) complete follow-up carriage studies (likely to be two annual carriage studies); (9) analysis of epidemiologic and laboratory results from follow-up carriage studies; (10); presentation of study results to local authorities, research community, and partners; and (11) publication of final report of study results.

Countries/Regions: This study should be conducted in an area with substantial prevalence of penicillin and/or sulfa resistance among pneumococci in order to efficiently determine the impact of vaccination on reducing colonization of resistant organisms (e.g., Asia, Eastern Europe, Alaskan villages, SE United States). Alaskan villages may be the ideal setting because of the anticipated widespread introduction of conjugate vaccines in the United States before other sites, the availability of baseline data on resistance, the availability of ongoing laboratory-based surveillance for invasive disease, and the fact that Alaskan villages reflect developing country settings with very high rates of respiratory and invasive pneumococcal diseases.

Partners: World Health Organization Vaccine and Biologics unit has already established committee to standardize nasopharyngeal carriage methods for use in vaccine trials; the Arctic Investigations Program has established baseline studies of pneumococcal serotypes and resistance; additional partners to be determined.

5.19 Title: Studies to Evaluate Behavioral and Policy Interventions to Improve the Use of Antimicrobials at the Household and Community Levels

Implementing Organizations: HIID/ARCH and MSH/RPM

Rationale: The 1997 International Conference on Improving Use of Medicines (ICIUM) marked a major milestone in international efforts to promote quality use of medicines by health providers and consumers, and to develop rational pharmaceutical policies. For the first time, there exist a consensus about appropriate methodologies for implementing and assessing interventions in these areas, coherent summaries of previous experience, as well as an agreed agenda of priority policy implementation and intervention research topics. Four organizations (WHO/EDM, INRUD, RPM, and ARCH) have collaborated to advance this agenda through a joint intervention research initiative, including a series of research proposal development workshops and a subsequent research program.

The overall goal of the post-ICIUM initiative is to increase the capacity for drug use intervention research and to stimulate a critical mass of research projects in the priority areas. The first phase of the joint initiative has focused on interventions targeting the practices of physicians, paramedics, and other health providers working in primary care, hospital, or retail pharmacy settings. A call for proposals on these topics by the sponsoring organizations resulted in 88 submissions that were reviewed and prioritized. The top-ranked 22 of the pre-proposals were invited to advance to the next stage of full proposal development, either independently or during one of two proposal development workshops that were held in 1998 in Yogyakarta, Indonesia, or Accra, Ghana. These projects are either already underway or in the process of further review.

USAID has been an active participant both in ICIUM and in the growing drug use intervention research initiative through its support to WHO/EDM and to the ARCH and RPM programs. Many of the priority topics for implementation and research identified at ICIUM are in areas of traditional USAID interest, such as improving pharmaceutical management of common childhood infections or reducing child and maternal mortality through more effective drug use in hospitals. In 1998, the USAID AMR Initiative enabled the expansion of the drug use portfolio to its current level by supporting the development and implementation of several proposals in the first phase that focussed on antimicrobial use by health providers.

The second phase of the joint initiative will emphasize the two remaining policy implementation and intervention research priority areas identified at ICIUM. First, proposals will be sought in the areas of improving patient compliance with antimicrobial therapy or improving patterns of antibiotic use within households or in the wider community. Participants at ICIUM recognized the critical need to inform and empower patients and consumers, who are the ultimate decision-makers in the use of medicines. Although consumer organizations and health educators have tried

individual education and media-based approaches to modify patient and community behavior, few have been adequately evaluated. Effective patient and consumer education about antibiotic use is a neglected area that requires focused research to identify promising strategies, and much greater advocacy.

The second ICIUM priority area to be highlighted in the call for proposals will be studies evaluating policies that affect the way antibiotics are used in the community. Studies that critically examine the impacts of common economic and pharmaceutical sector policies on use of antimicrobials are conspicuously lacking, despite the fact that these policies are widely employed. The topics and methods for these analyses could be diverse. Studies might examine, for example, the impacts of including or excluding a particular antimicrobial on a formulary or national essential drug list; a change in national or district-level policy regarding the antibiotic of choice for treating pneumonia; the impact of decentralization and local purchasing on appropriate use on antimicrobials; or the effects of increased patient cost-sharing for brand name or reserve antibiotics.

As emphasized at ICIUM, both community-focused and policy-analytic studies frequently require the use of multiple research methodologies, quasi-experimental designs, and longitudinal analyses. Practical examples of such methods and designs in developing countries are quite limited. This set of studies will add to experience in this area, and result in tools and approaches that can be employed in future studies.

Objective(s):

- To develop capacity to conduct and evaluate interventions or to evaluate policies intended to improve community use of antimicrobials
- To facilitate the design, implementation, and evaluation of at least five intervention and policy analysis studies that address key priorities in antimicrobial research identified at ICIUM
- To identify practical methods and tools for evaluating community-oriented interventions or policies that seek to improve antimicrobial use.

Description: This activity will follow the model for research capacity building and successful proposal development that has been employed by ARCH/ADDR for many years, and which formed the basis for the work in the first phase of the drug use intervention initiative.

During the first year, a request for proposals will be circulated through the research networks of the partners and other related organizations. Pre-proposals will be reviewed independently by each partner, and priorities for support based on the collective results of these reviews. At least six research teams will be invited to attend a proposal development workshop at which the research ideas will be clarified and developed into a full proposal. These proposals will be reviewed by external reviewers, revised according to their comments, and, when acceptable, approved for funding.

The six studies will be implemented by the research teams by the end of the first year or early in the second year. The typical study of this type will be two years duration. Technical support will be provided as required during the process of study implementation, with at least one visit per year b technical experts to each study team.

During the third year, research teams will be invited to participate in a data analysis workshop. Initial analyses of data will be completed, and research teams will prepare policy briefs for disseminating results of their studies at a local and national level. The works will be revised for publication in national and international scientific journals in order to maximize the value of the lessons learned.

Expected Outputs, Results and Progress Indicators: It is expected that this activity will result in the design, funding, and initiation of at least six investigator-initiated studies on the priority topics by the end of the first year; completion of the interventions and collection and cleaning of outcomes data by the end of the second year; and completed data analyses, study reports, and policy dissemination by the end of the third year.

Countries/Region: Countries will be determined by the results of a competitive review of submitted proposals. It is expected that at least one country will be included from Asia, Africa, and Latin America.

Partners: WHO Essential Drugs and Other Medicines Department (WHO/EDM); and the International Network for Rational Use of Drugs (INRUD).

5.20 Title: Home Management of Neonatal Sepsis by Village Health Workers and the impact on Neonatal Mortality and Colonization with Antibiotic-Resistant Bacteria

Implementing Organization: JHU/FHACS

Rationale: Neonatal mortality rates remain unacceptably high in developing countries. Almost half of neonatal deaths in developing countries are associated with infection, and 60% of deaths occur during the first week of life. Limited understanding of the causes of neonatal mortality in developing countries is based on studies of hospitalized infants that may not reflect causes of neonatal mortality in the community. In a recent study in Gadchiroli District, Maharashtra, India, Bang et al. trained village health workers (VHWs) to diagnose and manage sepsis in newborns and to provide perinatal and neonatal care. The net percent decline for neonatal mortality was 62% and for infant mortality 46%. The mortality due to sepsis was reduced by 76%. Although promising, the use of antibiotics in the community to reduce neonatal mortality must be shown to be effective in other settings, and the impact on the prevalence of antibiotic-resistant bacteria assessed.

Objective(s):
1. Evaluate the impact on neonatal mortality of management of neonatal sepsis by VHWs
2. Evaluate the impact on colonization with antibiotic-resistant bacteria of home administration of antibiotics by VHWs to neonates with suspected sepsis
3. Evaluate the cost-effectiveness of a community-based approach to neonatal care and the management of neonatal sepsis

Description: The project will be conducted in two countries. In each country, communities will be

randomized to control or intervention arms. Criteria for study sited selection include high rates of infant mortality and home delivery, poor access to health care, availability of VHWs and a minimum of 6000 live berths per year. With a baseline neonatal mortality rate of 50/1000, an individually-randomized study with 1605 newborns in each group would be sufficient to detect a reduction of 40% in the intervention arm. As this is a community-randomized trial, doubling the sample size should be sufficient to account for between-community variability. We anticipate enlisting 10-15 communities, and 3210 newborns, for each study arm in each country.

Baseline data to be collected during the first year will include: 1) neonatal mortality rates; 2) causes of neonatal deaths based on verbal autopsy reports; and 3) newborn care practices. VHWs from the intervention community will be trained in neonatal care, including the recognition and management of neonatal sepsis. To further improve neonatal survival, VHWs and Trained Birth Attendants (TBAs) in the intervention community will be instructed in:1) the recognition and management of complicated pregnancy; 2) appropriate hygiene during delivery and the immediate post-partum period; 3) neonatal resuscitation; and 4) newborn warming.

After completion of the baseline data collection and training, VHWs will perform regular home visits in the intervention community on days 1, 3, 7, 14, 21 and 28. If the birth weight is less than 2500 grams, home visits will take place daily until one month of age. VHWs will be trained to diagnose neonatal sepsis using the following criteria: 1) temperature greater than 38 C or less than 36 C; 2) poor feeding; 3) lethargy; 4) erythema and tenderness around the umbilicus; 5) a combination of diarrhea, vomiting and/or abdominal distention; and 6) severe pneumonia. Parents of infants diagnosed with sepsis will be encouraged to take the child to the nearest hospital. If not feasible, the VHW will initiate antibiotic therapy. The antibiotic regimen will be parenteral ampicillin and gentamicin, or oral cotrimoxazole and parenteral gentamicin. The VHW will maintain a record of the daily clinical status and outcome for each infant diagnosed with sepsis. VHWs will visit newborn infants in the control community within 24 hours of birth. If the infant weighs less than 2,500 grams, the mother will be advised to take the infant to the nearest hospital or health care facility. The VHW will visit the home and weigh the infant again at one month of age. A trained health care worker will perform a verbal autopsy to determine the cause of death for all infants who die.

Colonization with antibiotic-resistant bacteria will be assessed in a sub-sample of one month old infants during the baseline data collection period and at the end of the intervention. Nasopharyngeal and stool/rectal swabs will be obtained from one month old infants and cultured for penicillin-resistant *Streptococcus pneumoniae* and ampicillin-resistant *Escherichia coli*. Costs will be recorded during the training and intervention periods, and categorized as service costs or research costs. Anticipated costs include training, equipment, wages, incentives, drugs, supplies and transportation.

Expected Outputs, Results and Progress Indicators: Cause-specific neonatal mortality rates and rates of colonization with antibiotic-resistant bacteria during the pre-intervention and intervention periods will be compared for each community, and between the control and intervention groups. The cost-effectiveness of community-based neonatal care will be evaluated.

Countries/Regions: Proposed sites include Mali, India, Nepal and Haiti.

Partners: Society for Education, Action & Research in Community Health (SEARCH), Gadchiroli District, Maharashtra, India.

5.21 Title: Impact of IMCI Counseling Guidelines on Compliance with Antimicrobial Therapy in the Home

Implementing Organization: JHU/FHACS
Rationale: The integrated management of childhood illness (IMCI) approach developed by WHO and UNICEF is being adopted by an increasing number of developing countries as their primary intervention to improve facility and community-based management of sick children. The prescription of antimicrobials for sick children with bacterial infections is a key element of the IMCI approach. The IMCI clinical algorithm recommends oral antimicrobials and home treatment for sick children with clinical diagnoses of non-severe pneumonia, malaria, dysentery, and acute ear infections. The effectiveness of the IMCI drug counseling guidelines on compliance with antimicrobial therapy in the home has not been evaluated. This is a key programmatic issue. If sub-therapeutic treatment doses are being given in the home, then there is an increased risk of the development of antimicrobial resistance and an increased risk of mortality for the individual child. This study will determine the impact of IMCI counseling guidelines on compliance with antimicrobial therapy in the home, investigate barriers to compliance. This study will complement another study now being conducted in Uganda with USAID AMR funds by Johns Hopkins University and Institute of Public Health, Kampala, Uganda.

Objective(s):
1. To evaluate the impact of the IMCI treatment counseling guidelines on the number of sick children seen at Community Health Centers (CSCOM) that complete a full course of antimicrobial treatment at home.
2. To identify barriers to completing a full course of antimicrobial treatment in the home following IMCI Treatment counseling.

Description: Study Site The study will be conducted in sikasso Region, Bougouni District, Mali. For the purposes of this study, Bougouni District can be divided into 3 zones.
Zone 1: This comprises two rural arrondissements and the commune (urban area) of Bougouni where Save The Children USA has implemented a USAID BHR/PVC Child Survival grant from September 30, 1995 to September 29, 1999. Activities implemented under the grant included immunization, improved case management of diarrhea and malaria in health centers and in the home, nutrition including Vitamin A distribution, family planning and maternal health. There were no specific intervention activities related to acute respiratory infections.
Zone 2: This comprises 3 rural arrondissements where the Save The Children project will be expanding its activities through mission funding from USAID/ Bamako after the current child survival project in Zone 1 ends.
Zone 3: This comprises 6 other rural arrondissements that are not included in either of the Save The Children projects.

Study Design	Time 1	Time 2	Time 3
Zone 1		M I	M
Zone 2	M I	M	
Zone 3		M	

I=Intervention: Personnel in Health Centers receive a modified IMCI training course including the complete IMCI training on counseling of parents on how to administer the drug to the sick child.
M= Measurement: Measurement of reported doses of antimicrobials given in the home will be conducted. For children receiving antimicrobials for diarrhea or ARI at health facilities, home visits will be made after 5 days. Completion of the course of antimicrobials will be assessed by history and by counting antimicrobials remaining after 5 days. Exit interviews will also be conducted with a sample of parents of young children upon leaving the health facility. Respondents will be administered a brief survey about how long they waited, what happened in the appointment, what treatment they were told to take, etc.

Comparisons:
1) Comparison of Zone 2 at Times 1 and 2 and Zones 2 and 3 at Time 2 will show how much IMCI training of health personnel improves compliance in health facilities that had not otherwise been upgraded.
2) Comparison of Zones 1 and 2 at Time 2 will show how much better IMCI training is than the routine training implemented as part of many PVO child survival projects that include diarrhea and malaria case management.
3) Comparison of Zone 1 at Times 2 and 3 will show how much improvement results from IMCI training in facilities that have already had some upgrading.

Other data collection methods: A sample of 30 parents of young children will be administered a semi-structured interview on knowledge and perceptions of medications.

Countries/Regions: Save The Children USA is just completing a four year Child Survival Project (CS XI) (September 30, 1995 to September 29, 1999) in Bougouni District, Sikasso Region, Mali. Save The Children has developed local capacity to carry out operations research, and is eager to build on existing activities. While not providing funds, Save The Children will make some project resources available for the study.

Partners: Ministry of Health and Population Services (MSSP), Mali.

5.22 Title: Review of the Effects of Provider Reimbursement Mechanisms and Managed Care on the Use of Antimicrobial Drugs in the NIS and Developing Countries.

Implementing Organization: MSH/RPM

Rationale: National health reforms in the NIS and developing countries are introducing changes in health services organization, delivery, and finance. Social health insurance schemes are being implemented, principles of managed care applied, and incentive-based mechanisms to reimburse providers introduced. These changes are expected to influence provider and consumer behaviors in

support of cost-effective health systems. However, some changes may introduce new conflicts and unanticipated consequences. Changes in the ways providers are rewarded for providing services would be expected to alter prescribing practices and influence communication with patients about the appropriate use of drugs. Patients' decisions to purchase and consume a full course of antimicrobial drugs would be expected to be influenced, in part, by the way providers communicate with patients. The influence of health reforms on the use of antimicrobial drugs is extremely important because of the adverse clinical, economical and ecological consequences of inappropriate use and positive effects associated with appropriate use. It is critical to assess the impact of health reforms on the use of antimicrobial drugs so that countries can integrate lessons learned into not only the design of their national reforms but also in monitoring their impact. Provider or "supply side" responses will be the focus of this review. This study will build on a previous review undertaken by RPM that examined, among other things, the impact of patient charges (demand side interventions) on antimicrobial drug use.

Objective(s): To assess both positive and negative lessons learned on the impact of managed care and provider reimbursement mechanisms on the use of antimicrobial drugs in the NIS and developing countries by systematic analysis of findings from published and unpublished studies.

Description: A comprehensive and systematic review of published and unpublished studies on the impact of managed care and provider reimbursement mechanisms on the use of antimicrobial drugs in developing countries will be undertaken. An analytical framework will be developed to provide a structure for evaluating the impact of the above reforms (interventions) on the behavior of providers and consumers in use of antimicrobial drugs.
This review will build on the experience of other efforts to identify studies that assess the impact of interventions on drug use in general and antimicrobial use in particular. Previous approaches started from a general drug use perspective. This review proposes to identify relevant studies searching for studies on the impact of managed care and provider reimbursement mechanisms.

On-line search engines, and databases such as the INRUD Bibliography and the Cochrane Library will be used to identify relevant published studies and overviews. In addition, World Bank task managers and USAID contractors that work on health reform in the NIS and developing countries will be contacted to identify unpublished studies. Studies that will be included in the review will have the following characteristics:

1. Studies that focus on the use of antimicrobial drugs;
2. Studies that examine the impact of one or more of following interventions: managed care, provider payment mechanisms;
3. Studies that include an assessment of the impact of the intervention on the use of antimicrobial drugs;
4. Studies of these interventions in developing countries and the NIS.

Because it is anticipated that few rigorous studies will be identified, this review will also search for systematic overviews and relevant primary reports on the impact of managed care and provider reimbursement mechanisms on drug utilization in general and antimicrobials in particular, in North America and Western Europe. This study will then attempt to identify lessons learned from developed country experiences that should be considered in he potential implementation of such approaches in developing countries and the NIS.

Expected Outputs, Results and Progress Indicators: Outputs include a bibliography of published studies that meet selection criteria and a report on "The Effects of Provider Reimbursement Mechanisms and Managed Care on the Use of Antimicrobial Drugs in the NIS and Developing Countries". Results: policy makers in developing countries will have access to a framework and results that will help guide policy decisions in designing health reforms that encourage appropriate use of antimicrobial drugs. Progress Indicators: compilation of studies that meet criteria; analytical framework completed; literature review completed; and assessment of lessons learned completed.

Countries/Regions: Studies in Africa, Asia, Latin America and the NIS.

Partners: WHO/EDM.

5.23 Title: Assessing The Effectiveness of Client-Based Job Aids to Support Compliance with Antibiotic Treatment Regimens

Implementing Organization: QAP II

Rationale: Even when drugs are correctly prescribed and the patient/caretaker is counseled, the patient often forgets, prematurely discontinues, or interrupts the treatment regimen. This problem can be addressed through a combination of interventions: better communication and counseling of the patient, involvement of family or community members in the provision of care, follow up visits of community health workers, and job aids that directly support compliance by the patient/caretaker.

One of the support tools that has received attention in improving work performance is job aids. They have shown to 1) enhance performance by reducing errors caused by poor recall and faulty decision making, 2) promote compliance with standards, and 3) reduce costs of training and retraining. Job aids provide reminders, information as needed and substitute for experience or training. Several studies have shown the effectiveness of job aids on worker performance while client-based job studies are rare. Child nutrition cards maintained by mothers and instructions for preparation of ORS are exceptions. Hence information addressing the effectiveness of job aids to support patient or caretaker compliance with prescribing practices in developing countries is very limited, and additional research is warranted.

QAP's work on the design of job aids for health providers has been successful with low level health workers in developing countries. For example, health workers are able to properly diagnose malaria using a diagnostic kit and job aid, without additional training. The QAP is currently improving job aids for IMCI classification, treatment and counseling. This study proposes to use the same job aids design approach (named PETAL) for the development of client-based job aids to ensure proper use of antibiotics. The PETAL method includes obtaining input from end users and identifying their needs, looking at use under actual field conditions, detailing problems with job aid use and addressing them, before the job aid is supplied to end-users.

Objective(s): The objective is to develop and test job aids that can be used by clients and other caretakers to support compliance with antibiotic prescribing standards. The development and production costs of the job aids will also be examined.

Description: Determine scope: Select type of patients or caretakers. Determine scope of treatment plans (e.g. ARI among children). Assess client needs and problems: A brief formative study is undertaken to understand the needs of patients, the ability to use and read job aids, and additional support that can be provided by primary health providers.

Iterative testing of the job aid(s): QAP's quality design method (PETAL) is used to design the job aids, test the job aid with patients/caretakers, assess the results and receive feedback, then redesign and repeat the process until the job aid meets the needs of the patient or caretaker. The study will 1) measure improvements in correct use of antibiotics, as well as the patient's ability to effectively use the job aid, and 2) cost the of introduction and production of the job aid.

Expected Outputs, Results and Progress Indicators: The study will provide two or more client-based job aids (matched to specific diagnosis and antimicrobial prescribing protocols). One job aid could involve drug packaging while another might entail illustrated instructions on a form. Instructions for health providers regarding distribution and counseling of patients in the use of job aids will also be developed and included as study outputs. (These instructions may entail an additional provider job aid, depending on their needs.) The relative cost effectiveness of the job aids, as well as a strategy for introducing the job aids, will be presented in the research report.

Countries/Regions: The study will be completed in an African country where QAP has already been working with local counterparts to develop and test job aids such as Malawi and Zambia.

Partners: None.

5.24 Title: Improving Knowledge of Primary Care Physicians and Medical Students to Enhance Rational Prescribing of Antimicrobials through the Use of Established Drug Information Centers and Networks.

Implementing Organization: RPM/USP

Rationale: It is generally accepted that the misuse of antimicrobial drugs, resulting in part from a lack of appropriate drug use information, contributes to antimicrobial resistance. Based on the state of the art technical review of antimicrobial drug information in Russia, Nepal, Peru, and Ghana, USP has found that, in general, physicians lack concise up-to-date information on the use of antimicrobials, especially information on basic use, pharmacokinetics, pediatric and geriatric use, drug interactions, and treatment of side effects. In addition, more information is needed on appropriate perioperative infection prophylaxis; recommendations for adjustment of treatment regimens, e.g., parenteral to oral therapy, as the patient improves; and practical comparisons among antimicrobial agents, in particular within families of drugs. This review also found that there is very little drug information included in disease-specific standard treatment guidelines and that these guidelines tend to be poorly disseminated within countries.

Many countries, both developed and developing, have existing mechanisms for disseminating drug and therapeutics information. In most cases, the mechanism takes the form of drug information centers and networks. In fact, in research conducted by USP, it was found that the number of drug information centers in developing countries was increasing at a significantly faster rate than was the case for developed countries. The presence of these information centers and networks offers a unique opportunity to build grassroots efforts in educating health care professionals and students about the problem of antimicrobial resistance and in providing information to improve rational prescribing and use of antimicrobials.

Objective(s): To develop and evaluate prototype programs and materials for primary care physicians and medical students that would improve access to and understanding of information relating to the appropriate prescribing of antimicrobial agents.

Description: The proposed activity takes advantage of the ongoing RPM/USP activities in the Russian Federation and Moldova that relate to the provision of unbiased drug information. Specifically, the activities will build on the Russian translation/adaptation of the USP DI database and the establishment of the 12-member All-Russia Drug Information Network (ARDIN) and the Moldovan Association DRUGS. USP will work with members of ARDIN and the Moldovan Association DRUGS in the development of strategies for improving access to unbiased information about antimicrobial agents and in the creation of a training module for educating practitioners and students about their appropriate use. Concurrently, USP will work with PHARMEDINFO to publish a subset of the translated/adapted USP DI antimicrobial information monographs as an inexpensive reference for clinicians. The information will be condensed from the full monographs included in the Russian USP DI translation/adaptation. The format for the monographs will be developed through consultation with MOH officials and medical specialists, with input from ARDIN and DRUGS members. Where appropriate, local adaptations of the information will also be included in those materials developed for use in a specific geographic area. This process will not only serve to develop relevant, useful information but it will also raise awareness of the problem of antimicrobial resistance and build demand for appropriate training and the handbook. PHARMEDINFO will publish up to 20,000 copies of the handbook (depending on costs) and make them available for use in the training initiatives. It is anticipated that PHARMEDINFO will also make copies available at a subsidized rate for other clinical health care providers and will make the information available via electronic means, such as the Internet. The information will also serve as a resource for articles published in local and regional newsletters and bulletins that are developed by the drug information centers. Local and regional ARDIN members will coordinate use and evaluation of the teaching modules in their respective areas. After appropriate evaluation and revision, through a "training-the-trainers" approach, ARDIN members and the Association DRUGS will work to involve other information centers and institutions in Russia, Moldova, and potentially other NIS countries in effectively using the training module in their respective populations.

Expected Outputs, Results and Progress Indicators: Outputs include a strategy for improving access to unbiased information about antimicrobial agents; training module for teaching practitioners and students about the appropriate use of antimicrobial agents; prototype of handbook (Russian language) for clinicians on proper use of antimicrobial drugs; newsletter/bulletin articles. Results: Increased availability of and access to unbiased information on appropriate use of antimicrobials; increased number of DIC inquiries and responses relating to antimicrobial agents;

increased number of educational encounters relating to appropriate antimicrobial drug use; increased recognition of the importance of appropriate use of antimicrobial agents in an attempt to decrease antimicrobial resistance; increased knowledge among practitioners on appropriate antimicrobial prescribing. Progress indicators: availability of training module; availability of antimicrobials handbook; number of articles published in newsletters/bulletins; number of continuing education programs/participants; number of inquiries to DICs; improved prescribing of antimicrobials as determined by DUR.

Countries/Regions: Russia, Moldova, and other NIS countries as determined appropriate and feasible; potential for replication in other developing countries.

Partners: PHARMEDINFO, ARDIN, Association DRUGS.

5.25 *Title: Improving Patient Counseling and Dispensing Skills of Private Drug Retailers*

Implementing Organization: RPM/USP

Rationale: Most people in Nepal receive antimicrobial drugs directly from a private drug seller or chemist, usually without a prescription. Through USP's experience in Nepal, it has been observed that training requirements to become a licensed drug seller are minimal and no "refresher" training is required. Studies have shown that 68% of retailers in Nepal have no qualifications to sell drugs, let alone to prescribe. In one study, a therapeutically-appropriate full course of antibiotic treatment was received less than 25% of the time in retail shops. Using Nepal Infectious Diseases funding, RPM/USP has researched the antimicrobial drug knowledge and consumer counseling practices of licensed private sector drug sellers in Nepal in cooperation with the Nepal Chemists and Druggists Association (NCDA). Based on the results of this research the RPM project is developing a training intervention to improve patient counseling and dispensing of antimicrobial drugs used to treat the most common infectious diseases in Nepal. It is anticipated that the training intervention will become institutionalized as a part of the new legal requirements for becoming a licensed drug retailer currently being enacted by the Dept. of Drug Administration, HMG-Nepal and later rolled out to reach the majority of drug sellers in the country.

Objective(s): To reduce the spread of resistance to antimicrobial drugs used to treat the most common infectious diseases in Nepal (tuberculosis, malaria, STI's, pneumonia, diarrheal diseases, and kala-azar) by improving the skills of the major provider of antimicrobial drugs: private retailers.

Description: *Progress to date* includes research that has been done with the private sector retailers on the dispensing of and patient counseling for antimicrobials during FY 99 using funds from the 1998 allocation of ID money. The Manoff Group was contracted to develop a research plan, manage data collection and analysis and present findings and recommendations for an appropriate intervention. Manoff has worked in collaboration with New Era, a local Nepali research group. Preliminary results of the research show that:

- drug retailers dispense antibiotics for illnesses that do not necessarily call for antibiotic treatment;

- Drug retailers learn what antibiotics to dispense by observing what doctors prescribe for the same illness;
- Drug retailers do minimal, if any, labeling of medicines dispensed
- Drug retailers provide very little or no counseling to their clients when they dispense medicines to them;
- Drug retailers often sell less than the required/appropriate amount of antibiotics;
- To some extent, drug retailers see themselves as health care providers, not just businessmen;
- Drug retailers would welcome more training on drug selling;
- Drug retailers have very few, if any reference materials, and do not make effective use of those that they do have.

The findings from the qualitative portion of the research, which examines *why* the above findings are true, will inform the design and development of training and reference materials. For example, simple and easy-to-use reference materials on appropriate packaging and labeling may be indicated. In addition, support for drug retailers' encouraging clients to follow a full course of antibiotic treatment, instead of taking the medicine just until they feel better, may be appropriate.

In process: The training intervention is being developed and field-tested in collaboration with RPM/MSH. Core funds are being used to develop the draft training materials which can be adapted by other countries.

Planned for FY 2000: Core funds will also be used to develop a facilitator's guide for use by trainers of retailer-groups. Nepal ID funds will be used to evaluate the field test and revise the intervention and materials for Nepal. Additional core funds are requested to disseminate the training materials outside of Nepal as a model and to assist other countries with adapting/translating the model for local use through a sub-agreement mechanism. During FY 2000, the intervention will be evaluated and a rollout implementation phase will be planned. The group of drug sellers who go through the field-test training will be compared to a group of untrained drug sellers three months after the training. At the end of the field test, measures such as decreased AM drug sales, changes to more appropriate products, increases in repeat customers, improved patient/consumer counseling, will be used to evaluate impact. The DDA has already agreed, in principle, to include the training in the new requirements for drug retailer licensing being established now in Nepal.

Expected Outputs, Results and Progress Indicators:

- Outputs: Appropriate training materials developed which can be adapted for other countries.
- Results: DDA and NCDA staff trained to deliver the intervention and monitor improvement in drug retailer's knowledge and skills through post-training tests and surveillance mechanism, e.g., mystery clients.
- Indicators:
  - Decreased sales of drugs which have become less effective due to increasing resistance
  - Changes to more appropriate products
  - Increases in repeat customers
  - Improved patient/consumer counseling, e.g., more time spent with customer, accurate instructions provided on taking medicine, etc.

Countries/Regions: Nepal

Partners: Co-funders, USAID-Nepal and RPM/MSH; collaborating organizations, DDA, NCDA, DINoN, Manoff Group, and New Era.

5.26 Title: Technical Paper on Fixed-Dose-Combination (FDC) Drug Products

Implementing Organization: RPM/USP

Rationale: Although fixed-dose combination (FDC) drug products are generally discouraged in rational drug use strategies, there may be a place in therapy for such combinations when a patient must take multiple medicines and compliance is essential (e.g., treatment of tuberculosis or malaria). Combination drug therapy trials will soon be starting in several African countries to look at the efficacy of artemisinin derivatives in conjunction with other drugs for the treatment of malaria. Pending acceptable outcomes of these trials, the question of need and appropriateness of FDC therapy will have to be addressed. With many issues impacting the decision to accept FDCs (e.g., need for compliance, manufacturing standards, optimal dosing regimens, potential adverse reactions), RPM/USP believes it is necessary to identify and analyze the relevant issues and make this information available to procurement offices, manufacturers, essential drugs programs, health ministries, and other concerned parties before decisions on registration and production are made. Only in this way can a responsible plan of action be developed to ensure that safe, needed, high-quality products with proven therapeutic advantages are produced and distributed.

Objective(s): 1) To identify and analyze the issues surrounding use of FDCs. 2) To establish a generic protocol for issues that need to be addressed in the development of FDC products. 3) To examine the pros and cons of FDC products proposed for malaria therapy and make recommendations for what needs to be considered in developing optimal combinations and ensuring appropriate use.

Description: Fixed-dose combination (FDC) drug products are widely produced and marketed throughout the world. Such products represent a relatively simple way a drug manufacturer can extend its product lines (and profits) at a minimal cost. Although most FDCs would be considered as irrational therapy, there is some support for their use in cases where multiple-drug regimens can be reasonably standardized and compliance to therapy is absolutely essential. There is a considerable body of knowledge relating to FDCs. In addition, because of their widespread registration and availability, there is considerable experience with their use in patient care (either by a care-giver or through self-care).

This activity would focus on collecting available FDC information and experiences (by literature and policy review and through interviews with key individuals who are knowledgeable about FDCs), analyzing the issues presented, identifying the pertinent areas of concern, and subjecting the draft report to the scrutiny of experts and other interested parties. As part of the information/experience collection, selected FDCs on the market will be used as case studies/examples; policies of regulatory agencies and manufacturers will be explored; and research relating to the effect of FDCs on patient compliance/adherence will be reviewed. A group of experts

will be asked to serve as a reviewing body, with opportunity for public review and comment. The process will be open and transparent. Most of the discussions will make place via mail, telephone, and e-mail, with one face-to-face meeting of the individuals serving on the reviewing body scheduled towards the end of the deliberation period. The final draft document will be published for the review and comment of all interested parties.

Expected Outputs, Results, and Progress Indicators: Output: a state of the art examination of the issues surrounding the need for, risks/benefits of, and production and use of FDC drug products (with specific information relating to potential FDCs for use in malaria initiatives). Expected results: 1) an increase in informed decision-making relating to the need for and production and use of FDCs, in general. 2) Appropriate decisions relating to the development of FDCs for use in the prevention and treatment of malaria. 3) An increased understanding of the potential role FDC drug products may or may not have in rational drug therapy. Progress indicators: literature search with evaluation of papers, key person interviews, draft outline of paper, participation of wide body of experts, draft paper, USP panel consensus, public review, final paper.

Countries/Regions: Not applicable.

Partners: Not applicable.